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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/916,140	08/21/1997	MATTHEW P. SCOTT	CIBT-P04-203	2613

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ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/916,140	SCOTT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-71 and 74-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *61,62 and 81* is/are allowed.

6)☐ Claim(s) *63-71 and 74-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *29 January 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/28/03 has been entered.

Claims 72 and 73 were canceled and claims 78-81 were added as requested.

Claims 61-71 and 74-81 are pending and under consideration in this Office Action.

Drawings

Applicant has submitted drawings which are adequate for the purpose of examination.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed

to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at page 32, line 4, page 8; page 39, lines 8 and 9; and Table I on page 40; discloses nucleic acid sequences in excess of 9 bases that are not accompanied by a SEQ ID NO.** If these sequences are listed in the current Sequence Listing, then the specification should be amended to include the appropriate SEQ ID NO in each of the passages referred to above. If these sequences are not in the current Sequence Listing, then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Rejections Withdrawn

After further consideration the rejection of claims 62 and 72-75 is withdrawn. The disclosure at page 19, lines 4-15, page 20 to page 23, line 4 is considered to support screening assays for agents that decrease hedgehog signal transduction or increase patched activity in which cells with or without patched function by contacting the cells with test agents and measuring hedgehog signal transduction or patched activity. However, new grounds of rejection of claims 63-71, 76-80 are set forth below under 35 USC 112, first paragraph.

Applicant's amendments are sufficient to overcome the rejections of claims 61-63, 65, 68, 70, and 74-77 under 35 USC 102.

Claim Objections

Claims 61 and 62 are objected to. Each instance of "affect" should be deleted and replaced with "effect".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 63-71 and 74-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 63-71, 76-80 embrace methods that require a transcriptional control element that is stimulated by hedgehog signal transduction. The claimed genus embraces any transcription control element that is stimulated by any hedgehog signal, e.g. by Drosophila hedgehog, or vertebrate (sonic, Indian, and desert) hedgehogs. To adequately describe the claimed invention, the specification must disclose a representative number of such transcriptional control elements by complete structure or by relevant identifying characteristics. This can be done by reduction to practice, description of complete structure, or disclosure of relevant identifying characteristics (see the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov)).

The instant specification discloses a restriction map of about 10 kb of DNA upstream of the initiation codon of the Drosophila patched gene, and shows that several fragments of this DNA promote expression of beta galactosidase when incorporated into the genomes of Drosophila embryos. See Fig. 1, and page 26, lines 12-20. It is not clear from the specification that any of these fragments contain a hedgehog-responsive element, or whether transcription was controlled by other, non-hedgehog-sensitive, sequence elements in the DNA fragments. No sequence information for these fragments was disclosed.

The prior art teaches that, in Drosophila, the transcription factor Ci is necessary and sufficient to mediate the hedgehog signal, and that Gli1 is a analog of Ci that functions to mediate hedgehog signaling in mammals. See Altaba et al (Cell 90:193-196, 1997), sentence bridging columns 1 and 2 on page 193, and page 196, column 1, last three paragraphs. Muller et al (Development 127: 2999-3007, 2000) disclose that the binding site for Gli1 was published in 1990, so it is clear that those of skill in the art at the time of filing were aware of a transcription control element that is stimulated by hedgehog signal transduction, but this sequence was not disclosed in the instant specification as filed.

Shortly after the application was filed Krishnan et al (Science 278: 1947-1950, (12/12/97) identified by deletion analysis of a sonic-hedgehog-responsive gene a transcription control element stimulated by sonic hedgehog signal transduction. This element does not resemble a Gli1 site, and does not bind Gli1. See abstract, and page 1948, column 1, lines 17-34. This is evidence that the genus of transcription control elements stimulated by hedgehog contains variability and that the sequence characteristics of the various elements could not have been predicted at the time of filing. The evidence of record indicates that, at the time of filing, Applicant was aware of at most only a single transcription control element that is sensitive to hedgehog transcription, (i.e. the Gli/Ci binding site). Even if this sequence had been disclosed in the specification as filed, it would not be representative of the claimed genus, which clearly encompasses at least one other member that is dissimilar both in terms of structure as well as in terms of the transcription factor it binds. Because the

specification fails to disclose a representative number of species of the claimed genus by reduction to practice, structure, or relevant identifying characteristics, one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time of filing.

Claims 74-77 are reach-through claims that add method steps to those recited in claims 61, 62, or 63. The added method steps require preparing a formulation including an agent that decreases hedgehog signal transduction (claims 74 and 76), and administering the formulations to a patient (claims 75 and 77). As such, the claims are drawn to the genus of agents that decrease hedgehog signal transduction. These claims lack adequate written description because the specification as filed fails to disclose a single agent that decreases hedgehog signal transduction or increases patched activity in a cultured cell, and it fails to describe any relevant identifying characteristics such as a correlation between structure and function that is typical of species of the genus. The specification teaches that agents may be small organic compounds having a molecular weight of more than 50 and less than 2500 Daltons, and provides a non-limiting exemplary list of classes of molecules including peptides, saccharides, fatty acids, steroids, purines, and pyrimidines. This in no way provides sufficient guidance to one of skill in the art as to what structural features are necessary to provide the required function. As such, one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time of the application was filed.

Enablement

Claims 63-71 and 74-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As discussed above under written description, the claims require a transcriptional control element that is stimulated by hedgehog signal transduction, but the specification fails to clearly disclose such an element. The claims are broad, embracing any transcriptional control element with the desired function without limiting the sequence of the element. The prior art teaches that, in Drosophila, the transcription factor Ci is necessary and sufficient to mediate the hedgehog signal, and that a Ci analog, Gli1, exists in mammals. See Altaba et al (Cell 90:193-196, 1997), sentence bridging columns 1 and 2 on page 193, and page 196, column 1, last three paragraphs. The binding site for Gli1 was known prior to the time this Application was filed, but was not disclosed in the specification as filed. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, a transcriptional control element that is stimulated by hedgehog signal transduction is a critical element of the invention that cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure. Failure to disclose such an element results in a failure to meet the enablement requirement. It is noted that the specification teaches how to search for the required transcriptional control elements, e.g. at pages 21 and 22. However, a description of how to search for a particular sequence does not constitute an enabling disclosure of how to make that sequence, because such a disclosure contains no information as to the actual structural characteristics that provide the function required by the claims. As discussed above, the structure of transcription control elements that are stimulated by hedgehog signaling is unpredictable, because not all of the transcription factors involved in mediated hedgehog signaling were known in the art at the time of filing. As such, guidance as to where to search for the sequences with the required structural and functional characteristics provides only a starting point for further research that could ultimately discover such sequences.

As discussed above under written description, claims 74-77 are reach-through claims that add method steps to those recited in claims 61, 62, or 63. The added method steps require preparing a formulation including an agent that decreases hedgehog signal transduction (claims 74 and 76), and administering the formulations to a patient (claims 75 and 77). As such, the claims are drawn to the genus of agents that decrease hedgehog signal transduction. These claims lack enablement because the specification as filed fails to disclose a single agent that decreases hedgehog signal transduction or increases patched activity in a cultured cell, and it fails to describe any relevant identifying characteristics such as a correlation between structure and function that is typical of species of the genus. The specification teaches that agents may be small organic compounds having a molecular weight of more than 50 and less than 2500 Daltons, and provides a non-limiting exemplary list of classes of molecules including peptides, saccharides, fatty acids, steroids, purines, and pyrimidines. This in no way provides sufficient guidance to one of skill in the art as to what structural features are necessary to provide the required function. One might argue that it would not be undue experimentation to express and assay candidate agents individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors,

> such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. In view of the vast breadth of compounds disclosed in the specification from which candidate agents may be chosen, the failure of the specification to give any guidance as to what structural features might characterize agents that will inhibit hedgehog signal transduction, and the failure to generally to provide any theoretical framework that could be used by one of skill in the art to predict the structure of such agents, one of skill in the art would have to perform undue experimentation in order to practice the methods of claims 74-77 particularly in view of the unpredictable nature of the physiological art. One might argue that, if the methods of identifying an agent (claims 61 and 62) are enabled, then it is inconsistent to reject the dependent claims 74-77. This would be unpersuasive, because the methods of claims 74-77 differ from claims 61 and 62 in that they require an agent that was not described in the specification as filed. Claims 61 and 62 satisfy 35 USC 112, first paragraph inasmuch as the specification teaches how to make and use methods of identifying hedgehog antagonists. However, because the specification and prior art fail to disclose the particular structure of any such antagonist, one of skill in the art would have had to perform undue experimentation in order to make a composition comprising the agents, as required by claims 74-77. As indicated above, guidance on how to find a product is not equivalent to a positive recitation of how to make such a product.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 74-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 74-77 are reach-through claims that add method steps to those recited in claims 61, 62, or 63. The added method steps require preparing a formulation including an agent that decreases hedgehog signal transduction (claims 74 and 76), and administering the formulations to a patient (claims 75 and 77). Because the preambles of these claims require only identifying agents that decrease hedgehog signal transduction or that increase patched activity, it is unclear what is the purpose of the added steps such that it is unclear what are the metes and bounds of these claims.

Conclusion

Claims 61, 62, and 81 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the

application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

Richard Schnizer, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER